REMARKS

Entry of the foregoing and favorable reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. Section 1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendment, Claim 15 has been amended to recite that the polypeptide is expressed *in vivo* in muscle cells instead of "said muscle cells." Support for this amendment appears at least on pages 6 and 7 of the application as filed. Claim 20 has been added. Support for the terminology "distributed throughout the muscle mass" appears at least on page 7, lines 1 to 4 of the application as filed. Applicants submit that no new matter has been added via this amendment.

35 U.S.C. § 103(a)

1) Claims 15, 18 and 19 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Perricaudet et al in view of Quantin et all and Rice et al and further in view of Ordahl et al. For the following reasons, this rejection is respectfully traversed.

Perricaudet et al teach using adenoviral vectors under the control of the adenoviral major late promoter in association with the tripartite leader sequence to express a coding sequence. In this respect, Perricaudet et al teach that the intramuscular injection into mice of a β-galactosidase-encoding recombinant adenovirus resulted in an efficient infection of skeletal muscle cells.

There is no teaching in Perricaudet et al that another promoter other than the adenoviral major late promoter can be used in adenoviral constructs. There is no indication whatsoever what promoter was used when the β-galactosidase recombinant adenoviral vector was injected intramuscularly into mice and stained myotubes were detected indicated the ability of the recombinant adenovirus to infect skeletal muscle.

Furthermore, there is no teaching in Perricaudet et al that by using the adenoviral vector the polypeptide is expressed in muscle cells and is distributed throughout the muscle mass. There is no disclosure that the adenoviral vector can also be expressed in, for instance, cardiac muscle cells.

Quantin et al teach a β-galactosidase-encoding recombinant adenoviral vector under the control of a mouse skeletal α-actin promoter reinforced by an enhancer from a mouse myosin light chain gene (MLC1-3F).

Quantin et al disclose that β-galactosidase expression was detected in myogenic cells and cells obtained when fused myoblasts cultures were infected suggesting that the myotubes themselves may be infected. Figure 2 shows the infection of C2.7 myotubes and L6 myotubes.

There is no suggestion in Quantin et al that cardiac muscle cells can also be infected and hence by using the adenoviral vector the polypeptide is expressed in muscle cells and is distributed throughout the muscle mass.

Rice et al. disclose an E1-deleted adenovirus containing in place of the E1 sequences the RSV LTR fused to the cat gene. This vector was constructed as a control since the RSV LTR was known to be insensitive to tat. Cat activity was equivalently detected after infection of *tat*-expressing HeLa cells and the parental HeLa cells.

As pointed out by Applicants before, HeLa cells cannot be equated with muscle cells, since they are epithelium cells. The mere fact that the RSV LTR promoter fused to CAT is disclosed in this reference has no pertinence to whether the RSV LTR can be used to express a polynucleotide in muscle cells and the polynucleotide can be distributed throughout the muscle mass.

The newly cited reference of Ordahl et al (U.S. Patent 5,266,488) relates to the identification of the regulatory elements of the polynucleotide sequence, which comprises the chicken troponin T gene promoter (cTNT).

There is no disclosure in Ordahl et al of an adenoviral vector. Indeed, Ordahl et al teach using the plasmid pRSVcat as a control to compare expression with the cTNT promoters. Plasmid pRSVcat is thus only a reporter plasmid, which cannot be compared in size with an adenoviral vector, which is much larger.

Furthermore, the cardiac and skeletal muscle cells were treated before hand with 15% glycerol and sodium phosphate (see, column 9, lines 6 to 21 of Ordahl et al). A person skilled in the art would appreciate that this procedure induces holes in the cell membranes permitting easy entry of the plasmid. Although expression in treated muscle cells was in fact achieved it was achieved *in vitro*. Moreover, a person skilled in the art

would realize that this achievement could in no manner could be equated with the adenoviral vector in the present invention, which as demonstrated in the specification, the polypeptide was expressed throughout the muscle mass with no additional treatment of the neither skeletal nor cardiac cells.

The Examiner deems that it would be obvious for the person skilled in the art to use the teachings of Perricaudet et al and Quantin et al to construct a defective adenoviral vector which is deleted in the E1 region for introducing genes and use the well known promoter of RSV LTR taught in Rice et al for expression in muscle cells as taught by Ordahl et al, since Ordahl et al "teach the well known use of the RSV LTR promoter to drive expression in muscle cells so as to ensure high levels of expression of the gene product."

However, Ordahl et al only teaches the expression of a small plasmid using the RSV LTR promoter in isolated muscle cells, which were previously treated to allow easy entry of the small plasmid into the isolated muscle cells. This, Applicants submit, would not provide any guidance to one skilled in the art whether a large adenoviral vector could in fact enter muscle cells and be distributed throughout the muscle mass (in cardiac and skeletal muscle) without previous treatment as demonstrated in the present invention. There simply would be no expectation of success from the teachings of the prior art that a defective adenoviral vector recited in Claim 15 could in fact penetrate the epithelial sheath surrounding muscle cells and be distributed throughout the muscle mass.

Lacking any teaching of the above in the prior art, Applicants submit that this rejection cannot be maintained. Therefore withdrawal of this rejection is respectfully requested.

2) Claim 17 has been rejected under 35 U.S.C. § 103(a) as being obvious over Perricaudet et al in view of Rice et al and Ordahl et al and further in view of Nabel et al. For the following reason, this rejection is respectfully traversed.

Perricaudet et al, Rice et al and Ordahl et al were discussed extensively above and the same arguments apply in this rejection. More specifically, as stated above, Perricaudet et al fail to disclose the specific promoters now recited in the claims. Rice et al, although disclosing the RSV (LTR) promoter in an adenoviral vector having the E1 region deleted, the expression was in *tat*-expressing HeLA cells, which are not muscle

cells, but are an epithelial-like cell line. Ordahl et al fails to teach that an adenoviral vector having a RSV LTR can penetrate non-treated muscle cells. None of the cited references disclose, teach or even suggest that the polypeptide expressed by the defective adenoviral vector can be distributed throughout the muscle mass.

Nabel et al does not remedy the deficiencies of the other references with respect to Claim 17. Applicants submit that Nabel et al is quite complicated to read and ascertain exactly what the content of the many inventions disclosed therein is about. Applicants also submit that since so many different embodiments of the invention are disclosed in this issued U.S. Patent that it is only logical that the many specificities disclosed under each embodiment cannot be freely interchanged, but are specific to certain embodiments disclosed under the very specific headings in Nabel et al.

The Examiner refers to column 4, lines 40 to 68 and Columns 5, 8-9, and 11 of Nabel et al and deems that this reference teaches "the use of adenoviral vectors to express genes with thrombolytic properties (i.e., plasminogen activator, streptokinase etc.) in muscle cells *in vitro* and *in vivo* so as to treat ischemic disease." Applicants respectfully disagree that a person skilled in the art could come to this same conclusion as the Examiner, since there was no demonstration that a polypeptide could be expressed in muscle cells via a defective recombinant adenoviral vector in Nabel et al.

The reference to Column 4, lines 40 to 68 relied upon by the Examiner discloses the instillation of cells producing proteins via a catheter, which are instilled in various organs (Column 5 lines 9 to 20) or for delivery to the parenchymal tissues (Column 5, lines 35 to 48).

At column 4, line 49, smooth muscle cells producing proteins are one type of cells that may be instilled by the catheter.

To treat ischemic diseases, Nabel et al at column 5 suggests the introduction of angiogenic factors into the coronary circulation. But angiogenic factors such as FGF, IL-8, VEGF, EGF and the like, are not thrombolytic.

Thus, there is no teaching at either column 4 or 5 that recombinant vectors *per se* can be administered such that they are expressed in muscle cells.

However, Columns 7 and 9 of Nabel et al teach the "B. Introduction of recombinant genes directly into cells of the wall of a blood vessel or perfused by a

specific circulation *in vivo*...." (see, Title in last paragraph of column 7). This section specifically teaches the use of recombinant vectors *per se* and not instilling cells which express the recombinant vector. However, for the introduction of the recombinant vectors *per se* a high pressure catheter must be used. The high pressure catheter is necessary to "optimize the interaction of vectors with cells in adjacent vascular tissue" (Column 8, lines 45-46) and thus causes "the vector to migrate through the blood vessel walls into the surrounding tissue" (Column 8, lines 56-58). Note that with this high pressure catheter retroviruses are the only recombinant vector used as evidenced at Column 8 lines 36 to 46.

An additional method under this section in Nabel et al discloses injecting the recombinant vector *per se* into a capillary bed (Column 8, line 58-61). However, the only exemplification of this method in Nabel et al is with respect to tumors.

Yet another method described provides a method for the use of growth factors, which are delivered locally by catheter or systemically (Column 8, lines 47-52). It is in this paragraph that adenoviruses are referred to. But this paragraph refers to the delivery of growth factors only. There is no disclosure that adenoviruses can be used in conjunction with the high pressure catheters in this section.

Thus, there is no teaching in Nabel et al of using an adenoviral vector *per se* for delivering this vector to muscle cells. There is also no teaching that thrombolytic materials can be introduced with the high pressure catheter in this embodiment.

In fact, the only place where thrombolytic proteins such as plaminogen activator, streptokinase and the like are described at column 11, which is under the section entitled "Obtaining the Cells Used in the Invention." Column 11 clearly relates to treating ischemic diseases using cells and not the vector alone. More specifically it is stated throughout column 11 starting at line 30 the following:

> The present invention provides for the genetic alteration of cells as a method to transmit therapeutic or diagnostic agents...
>
> The range of recombinant proteins, which may be expressed in these cells..such as tPA...

For example for the treatment of ischemic diseases (thrombotic diseases), genetic material; coding for tPA or modifications thereof, urokinase or streptokinase is used to transform the cells.

Thus, there is no teaching that thrombotic agents can be inserted into a defective adenoviral vector and be used to treat ischemic diseases. In fact, the only place in which muscle cells are elaborated in the entire specification, besides the general mention at column 4, is at column 12 with respect to treating tumors using cell mediated gene transfer.

Thus, a person skilled in the art would in no certain terms ascertain from Nabel et al the use of a defective adenoviral vector encoding a thrombolytic agent *per se* to treat ischemic diseases, especially since there is no specific example showing that this recombinant vector can in fact be expressed in muscle cells. The skilled artisan would not have any expectation of succeeding by using a defective adenoviral vector encoding a thrombolytic agent *per se* to treat ischemic diseases, which thrombolytic agent is expressed throughout the muscle mass.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Obviousness Type Double Patenting

Claims 15 and 17 to 19 have been rejected under the judicially created doctrine of obviousness-type double patenting. Applicants request that this rejection be held in abeyance until there is allowable subject matter. At that time, Applicants will proceed by filing a Terminal Disclaimer.

35 U.S.C. § 112 2nd Paragraph

Claims 15 and 17 to 19 have been rejected under 35 U.S.C. § 112, second paragraph, since there is no antecedent basis for "said muscle cells." Claim 15 has been amended to recite "muscle cells, which should render this rejection now moot.

Summary

From the foregoing favorable action in the form of Notice of Allowance is respectfully requested and earnestly solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Claim 15 has been amended as follows:

15. (Forth time Amended) A composition comprising (i) a non replicative recombinant adenoviral vector wherein said no replicative recombinant adenoviral vector comprises a heterologous polynucleotide sequence encoding a polypeptide, which polynucleotide sequence is inserted into a deleted E1 region of said no replicative recombinant adenoviral vector and is under the control of a promoter selected from the promoter contained in the Long Terminal Repeat of Rous Sarcoma Virus, the promoter of the IE gene of cytomegalovirus, the Mouse Mammary Tumor virus inducible promoter and the metallothionine promoter wherein said polypeptide is expressed *in vivo* in[said] muscle cells and is distributed throughout the muscle mass;
and (ii) a pharmaceutically acceptable carrier.

Claim 22 is new.